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PTO/SB/16 (10-01)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

Express Mail Label No.	

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Bao-Jian	Li	Huston, Texas
Patrick Y.	Lu	Rockville, Maryland

☒ *Additional inventors are being named on the 1 separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

siRNA Oligo Cocktail for Treatment of Cancer, Infectious and Inflammatory Diseases

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 27 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☐ Other (specify)

☒ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE _____ Date February 6, 2004

TYPED or PRINTED NAME Paul M. Booth REGISTRATION NO. *(if appropriate)* 40,244

TELEPHONE 202-912-2000 Docket Number: 38147-0045

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Docket Number	38147-0045

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Martin C.	Woodle	Bethesda, Maryland

Number 2 of 2

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Complete if Known	
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FEE CALCULATION

1. BASIC FILING FEE

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1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
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2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =	0	x		=	0
Independent Claims		-3** =	0	x		=	0
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Large Fee Code	Entity Fee ($)	Small Fee Code	Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	**Reissue independent claims over original patent
1205	18	2205	9	**Reissue claims in excess of 20 and over original patent

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1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBMITTED BY

Name *(Print/Type)*	Paul M. Booth	Registration No. *(Attorney/Agent)*	40,244	*Telephone*	202-912-2000
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Complete *(if applicable)*

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siRNA Oligo Cocktail for Treatment of Cancer, Infectious and Inflammatory Diseases

Inventors: Bao-Jian Li
Patrick Y. Lu
Martin C. Woodle

Field of Invention

The invention relates to concepts, methods and compositions for using siRNA oligo cocktails (siRNA-OC) as therapeutic agents for prevention and treatment of cancer, and other diseases such as infectious diseases and inflammations.

Background

Human disease often is a complicated pathological process. Many human diseases are caused by abnormal over expression of disease causing or disease control genes from the human body or from foreign infectious organisms. Cancer, autoimmune diseases and infectious diseases represent these type of diseases.

Cancer:

Cancer often is caused by multiple genetic factors and environmental hazards. Inherent oncogenes and mutation of protooncogenes often contribute predominately to various cancers. Many cancer genes are well characterized: K-ras, c-Myc, a-raf and Bcl-2, etc. Over expression of various growth factors, FGF, VEGF, PDGF, EGF, and mutant tumor suppressor, Rb and p53, typically characterize malignant tissues. Cancer or pre-cancerous growth is frequently a consequence of proliferative cellular pathologies and generally refers to malignant tumors. Malignant tumors penetrate and destroy local tissues. Some malignant tumors may spread throughout the body via blood or the lymphatic system, and their unpredictable and uncontrolled growth makes malignant cancers dangerous, and fatal in many cases. Such tumors are not morphologically typical of the original tissue and are not encapsulated. Malignant tumors commonly recur after surgical removal. Accordingly, treatment of proliferative diseases ordinarily targets proliferative cellular activities such as occur in malignant cancers or malignant tumors with a goal to intervene in the proliferative

processes. Certain cellular biochemical pathways are activated at different stages of the proliferative processes.

The importance of tumor angiogenesis has been widely accepted for its role in the growth and development of solid tumors. It is now recognized that angiogenesis is not only essential for tumor growth, but is also implicated in the initial progression from a pre-malignant tumor to an invasive cancer, and in the growth of dormant micro metastases into clinically detectable metastatic lesions. Angiogenesis modulation with novel biological agents to inhibit pro-angiogenic factors has been one of the most attractive approaches for clinical development. Studies have demonstrated the importance of microvessel density for malignant progression in breast cancer, underscoring the importance of angiogenesis in this type of tumor. Anti-angiogenic molecules can fall into five main categories according to their mode of action: 1). Inhibitors of pro-angiogenic growth factors and their corresponding receptors, such as vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR2, FLK1/KDR), basic fibroblast growth factor (bFGF) and FGF receptors and platelet-derived growth factor (PDGF); 2). Protease inhibitors that prevent the breakdown of the surrounding matrix, which is needed for blood-vessel growth; 3). Endogenous inhibitors of angiogenesis, such as endostatin; 4). Inhibitors of cellular adhesion molecules and 5). Molecules with undefined mechanisms.

Many other pathways play very critical roles in tumor growth, such as Growth factors, Cytokines, Kinases and Transcription factors. Many of the factors involved in the related pathways over-express in tumor tissue, and may be good targets for siRNA-mediated knockdown for cancer treatment. Down regulation of multiple cancer causing genes either from the same pathway or different pathway with multiple siRNA inhibitors, ***at least three according to an embodiment,*** can achieve much stronger anti-cancer efficacy for the treatment. Present cancer treatments often involve combination of different therapeutic approaches, and drug modalities.

Inflammatory diseases

Rheumatic diseases (like rheumatoid arthritis, scleroderma, lupus, polymyositis, dermatomyositis, fibromyalgia, psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, and juvenile rheumatoid arthritis) are most common autoimmune diseases. These diseases include serious debilitations that affect over 1% of the population in the developed world, and accounting for millions of patients

worldwide. The disease may arise from a local inflammatory reaction, causing pain and impairing normal organ functioning affecting patients' daily activities. Several treatments exist to suppress the inflammatory episodes that are the hallmark of these diseases. Unfortunately, these agents can lack efficacy or cause severe side effects and tolerance to their therapeutic action can occur. A new treatment for rheumatic diseases that is both potent and avoids side effects or is able to add additional benefit to other treatment options (like corticosteroids, antibodies, antisense, gene therapy, soluble receptors, decoy receptors, receptor (ant)agonists, etc.) would mean a significant health benefit. Using siRNA inhibitor to knock down over expressed TNF, IL-1 and their receptors in the mammalian cells can be effectuated. By knocking down several proteins at the same time that are implicated in disease progression the symptoms may be alleviated.

Eye disease, Ocular neovascularization (NV) is an abnormal proliferation of new blood vessels within the eye, is an early pathological step of many eye diseases and is the most common cause of permanent blindness in the United States and Europe. Several major eye diseases promote the abnormal neovascularization and resulting further damage to the eyes.

Diabetic Retinopathy (DR) occurs when damage to the tiny blood vessels which provide oxygen to the retina become damaged. The damage allows blood and fluid to escape into the retina and can also result in new blood vessel growth. These new vessels are even more fragile and frequently bleed into the vitreous. Patients with the most serious form of DR are at a substantial risk for severe visual loss without treatment. Here the neovascularization results from the disease and even exacerbates matters, as caused by multiple unwanted expressions of certain disease genes.

Ocular neovascularization (NV) is abnormal proliferation of new blood vessels within the eye, and often is an early pathological step of many eye diseases. This abnormality is the most common cause of permanent blindness in United States and Europe. There are several major eye diseases promoting the abnormal neovascularization and resulting further damage to the eyes.

Diabetic Retinopathy (DR) occurs when damage to the tiny blood vessels which provide oxygen to the retina become damaged. The damage allows blood and fluid to escape into the retina and can also result in new blood vessel growth. These

new vessels are even more fragile and frequently bleed into the vitreous. Patients with the most serious form of DR are at a substantial risk for severe visual loss without treatment. Here the neovascularization is a consequence of the disease and may even make matters worse.

Infectious diseases

Many infectious diseases have claimed human lives throughout the human history. The recent SARS epidemic in China and Canada has killed hundreds of people. Scientists in many laboratories in Asia, Europe and North America have been working on the cause of SARS around the clock. A previously unrecognized coronavirus in patients with SARS has been isolated, sequenced and tested in a monkey model. This new coronavirus, which is the leading candidate for causing SARS, has been named SARS coronavirus by the World Health Organization. SARS coronavirus is a sense and single stranded RNA, and can cause one of the most prevalent infections in humans. The virulence of SARS coronavirus results from i) its easy spread by aerosol and other person-to-person contacts, ii) its ability to escape from protective immunity by frequent changes in viral antigens (antigenic drift, like influenza virus), and iii) the sharp emergence of new virulent strains of the virus by, maybe, reassortment or mixing of RNA segments between viruses from two different species (antigenic shift). The threat of this new strain of SARS coronavirus is so severe because, despite intensive efforts, no effective therapy or vaccine is yet available for prevention and treatment of the SARS coronavirus infection. SARS CoV proprotein replicase 1 (pp1) is the first and only gene product expressed using the viral RNA genome as template. The pp1a and pp1b (Figure 1a) are further processed into approximate one dozen non-structural proteins. The nsp-1 is probably a proteinase important for the maturation of viral proteins. The nsp-9 is a RNA dependent RNA polymerase that catalyzes the synthesis of viral RNAs.

siRNA duplex inhibitors

Use of RNA interference (RNAi) has been developing rapidly in cell culture and studies with model organisms such as Drosophila, C. elegans, and zebrafish. Studies of RNAi have shown that long dsRNA is processed by Dicer, a cellular ribonuclease III, to generate duplexes of about 21 nt with 3'-overhangs, called short interfering RNA (siRNA), which mediates sequence-specific mRNA degradation. As

RNAi was chosen as the "Breakthrough of the Year 2002" by *Science*, scientists believe that understanding the mechanisms of RNAi and its rapidly expanding application represent a major breakthrough during the last decade in the field of biomedicine. Use of siRNA duplexes to interfere with expression of a specific gene requires knowledge of target accessibility, effective delivery of the siRNA into the target cells, and, for some biological applications, long-term activity of the siRNA in the cell.

Summary of the Invention

In an embodiment, overexpression of VEGF proteins and/or their receptors is alleviated by, knocking down pro-angiogenesis genes, and combining multiple siRNA inhibitors for a strong effect. In an embodiment, a viral infectious disease is treated by knocking out one or more viral genes or by modulating the expression of a patient' cytokine genes. In an embodiment, such gene knockdowns inhibit ocular neovascularization, which is a major cause of blindness, and combats blindness.

Another embodiment inhibits SARS CoV RNA transcription and/or replication by targeting nsp-1 and nsp-9 coding regions with siRNA sequences. In an embodiment, the Spike protein which locates on the surface of a virion is inhibited. In an embodiment, tropism, receptor recognition, cell adsorption, and/or induction of neutralizing antibody is affected. In another desirable embodiment the Spike coding region is targeted and such targeting blocks or inhibits the spread of viral infection. In an embodimemt, the term "target" or "targeting" in this context means that the siRNA inhibits replication and/or transcription of the targeted sequence perceptibly (measurably, determined by experimentation with a statistical confidence of at least 95%). In another embodiment, "target" or "targeting" means that the siRNA binds specifically to a desired target. In the latter case, the affinity constant may exceed, 1000, 10,000, 1000,000 or more.

In another embodiment, these three viral mRNA are blocked, which inhibits viral protein production and results in inhibition of viral infection and replication. It was demonstrated that siRNA duplexes, which targeting these regions, indeed inhibit the SARS coronavirus infection and replication in non-human primate cell culture. It also was demonstrated that combination of the active anti-SARS siRNA duplexes is more effective than the single siRNA duplex.

An embodiment provides a composition of two or more siRNA duplexes, wherein each duplex targets a different gene or gene product. and wherein the composition inhibits a disease process caused by abnormal over expression of at least one of the targeted gene or gene product by formation of a siRNA duplex. Another embodiment provides a composition that comprises at least three gene sequences including three open reading frames and three mRNAs. Yet another composition provides a method for ameliorating a disease caused at least in part by over expression of one or more disease genes as described herein, comprising providing a composition of two or more siRNA duplexes, wherein each duplex targets a different gene or gene product. and at least one of the targeted gene or genes is a disease gene. Yet another embodiment provides a composition as described herein for treating SARS coronavirus infection, comprising siRNA-OC that comprises one or more siRNA target sequences corresponding to: Spike protein, 21553-21573, aagctcctaattacactcaac; Nsp-9, 13530-13550, aaggatgaggaaggcaattta; nsp-10, 17544-17564, aaggataagtcagctcaatgc; nsp-13, 20843-20863, and/or aactggcacactacttgtcga. Yet another embodiment provides composition as described in any of claims 1-9 for treating ocular neovascularization, comprising one or more siRNA duplexes: selected from the group consisting of mVEGFAa, AAGCCGTCCTGTGTGCCGCTG; mVEGFAb, AACGATGAAGCCCTGGAGTGC; mVEGFR1a, AAGTTAAAAGTGCCTGAACTG; mVEGFR1b, AAGCAGGCCAGACTCTCTTTC; mVEGFR2a, AAGCTCAGCACACAGAAAGAC; mVEGFR2b, AATGCGGCGGTGGTGACAGTA. Yet further embodiments will be appreciated by a reading of the specification.

Detailed Description

A desirable embodiment provides a therapy of administering siRNA via optimized local and systemic delivery methods. An advantage of using siRNA as a therapeutic agent is the specificity, stability and mechanism of action. Without wishing to be bound by any one theory of this embodiment of the invention, it was thought that each 21 nt double-stranded RNA oligo has its unique sequence specificity, and thus a combination of multiple siRNA duplexes can down regulate multiple target genes, resulting in a synergistic effect. Following this thinking, several combinations

of various siRNA duplexes targeting different genes, were tested for inhibition of expressions of either endogenous or exogenous genes. In particular, combinations of at least three siRNA duplexes targeting at least three genes for inhibition of disease processes successfully were evaluated.

In an embodiment, siRNA duplexes, or 21 nt double-stranded RNA oligos, are employed for gene expression knockdown. Desirably, regardless of the targeted genes, all may be synthesized as a similar chemical form. Accordingly, in an embodiment, the metabolic pathways of a treatment modality share one or more common features. In an embodiment, the combination of multiple siRNA duplexes in one drug dose does not induce an unexpected toxic side effect.

In another embodiment, a combination of multiple siRNA duplexes that target different genes involved in a disease pathology was found to present a much better therapeutic effect than using single siRNA duplex, that targets only one gene involved in the disease pathology, at the same dosage. This result clearly demonstrated synergistic effects of multiple gene knockdowns.

Another embodiment alleviates ocular neovascularization, which is the typical pathological symptom of many eye diseases. siRNA duplexes were designed that target murine VEGF A, VEGF R1 and VEGF R2 genes, as inhibitors that knock down corresponding genes and to block the angiogenesis process. These siRNA were delivered separately, and significantly inhibited infection induced angiogenesis, with either locally or systemic deliveries. However, administration of a combination of duplexes targeting all three genes was found to be much more effective in inhibiting the angiogenesis process.

Inhibition of SARS virus infection and replication in fetal rhesus kidney cells (FRhK-4) revealed 4 siRNA duplexes that target respectively, the non specified proteins (nsp-1, nsp-9 and nsp-10) and Spike protein. This showed strong prophylactic effects on viral infection (cells first being transfected with siRNA and then infected with the virus), but relatively weaker effects on the therapeutic effects (cells first infected with the virus and then transfected with siRNA). When

combinations of various active siRNA duplexes at different ratios were used, the therapeutic effects were significantly improved.

AN siRNA oligo cocktail (siRNA-OC) was studied having at least three siRNA duplexes targeting at lease three genes, to down regulate the expression of disease causing or disease control genes. The combination of siRNA oligos can provide equivalent or better effects on targeted diseases such as an eye disease. The proportion of each siRNA component can be altered depending the needs for effective down regulation of the targeted genes and disease status. An embodiment provides a siRNA-OC formulation that contains at least 3 siRNA duplexes. The number of siRNA duplexes in other embodiments can be more, for example, from 4 to 5, 6, 7, 8, 9, 10, or more.

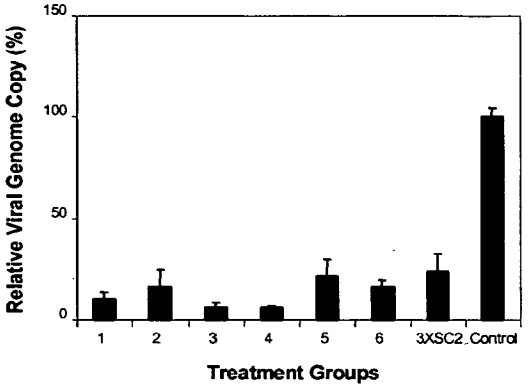
In an embodiment, targeted disease causing genes can be endogenously expressed genes or genes from an infective bacteria, virus andor protozoa, etc. The chemical form of siRNA duplexes can be same or different. The siRNA-OC can be delivered either locally or systemically. The siRNA-OC can be used for prophylactic effects, therapeutic effects, or both. The siRNA-OC can be used for treatment of cancer, autoimmune and inflammatory diseases. The siRNA-OC can be delivered in Saline solution or other solutions: liposome, polymer and nanoparticles. The siRNA-OC can be in a mixture or in powder form. The siRNA-OC also may be combined with another drug substance.

Examples:

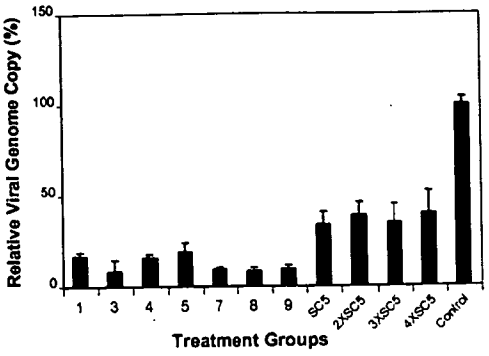
Example 1. Prophylactic effect of multiple siRNA combination for inhibition of SARS

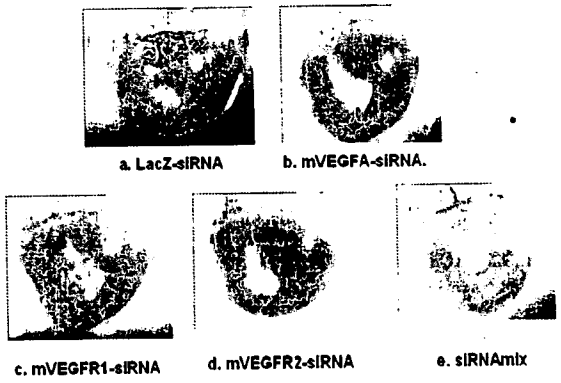
A coronavirus infection and replication in fetal rhesus kidney cells was made (FRhK-4). See Figure 1. Prophylactic effects of combined siRNA duplexes specific to SARS CoV were evaluated on this infection. A strategy of a combination of active siRNA duplexes to achieve stronger inhibition of viral replication was tested. FRhK-4 cells were transfected and infected as described in Figure 2. At 36 hours post viral infection, the cells and culture medium were collected for QRT-PCR and measurement of $TCID_{50}$. A combination of the active siRNA duplexes reduced the

viral genome copy. The inhibition effects of the combined siRNA duplexes were measured with real-time Q-RT-PCR and resulted in stronger inhibition than that from the single siRNA. A time course study was carried out using the combined SC2 and SC5 siRNA. The prophylactic effect of combined siRNA against SARS virus was well maintained up to 72 hours post transfection. The number of combination groups: are: 1: SC2 + SC5; 2: SC2 + SC5 + SC4; 3: SC14 + SC15; 4: SC14 + SC5; 5: SC14 + SC2; 6: SC5 + SC14 + SC15; 3xSC2: 0.9 μg of SC2 siRNA/well; 3XSC5: 0.9 μg of SC5 siRNA/well and Control: negative control without siRNA transfection.



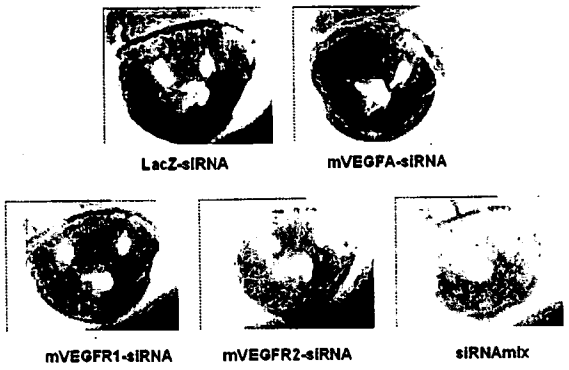
The therapeutic effects of combined siRNA duplexes on the SARS coronavirus infection and replication in the fetal rhesus kidney cells (FRhK-4) also was evaluated. See Figure 2, which shows therapeutic effects of combined siRNA duplexes specific to SARS CoV. Combinations of the active siRNA duplexes were tested for their therapeutic potentials. FRhK-4 cells were infected with 3 PFU/cell of SARS CoV followed by transfection with various combination of siRNA duplexes one hour p.i. At 36 hours post transfection, cells and culture medium were collected for Q-RT-PCR and measurement of viral titer, respectively. A. Combined siRNA duplexes were able to improve the inhibition effect significantly ($P<0.05$) measured by reduction of the viral genome copies in the cytoplasm of infected FRhK-4 cells. 1: SC2 + SC5; 3: SC14 + SC15; 4: SC14 + SC5; 6: SC14 + SC2; 7: SC5 + SC15; 8: SC2 + SC5 + SC14 + SC15; 9: SC2 + SC5 + SC14; 2XSC2: 0.6 μg of SC2/well; 2XSC5: 0.6 μg of SC5 siRNA/well; 3XSC5: 0.9 μg of SC5 siRNA/well; 4XSC5: 1.2 μg of siRNA/well and Control: negative control without siRNA transfection.





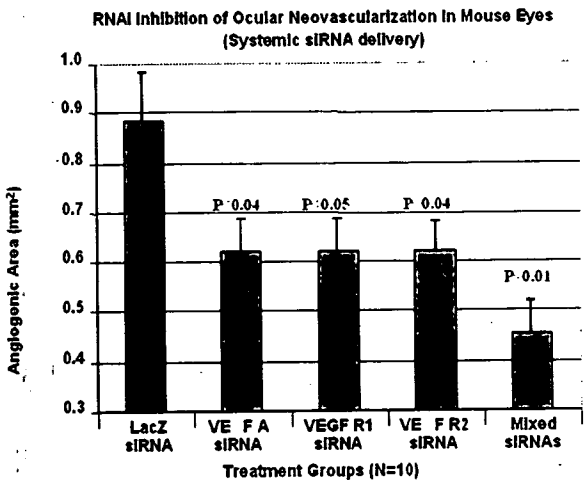
Also evaluated was the siRNA-mediated inhibition of murine pro-angiogenesis genes with either control siRNA (LacZ-siRNA) or mVEGF A-siRNA, or mVEGF R1-siRNA or VEGF R2-siRNA, or combination of all siRNA duplexes targeting all three genes. See Figure 3, which shows the local delivery of siRNA to inhibit NV in Mouse Eyes. In this study, siRNA duplexes (two for each gene: mVEGF, mVEGFR1 and mVEGFR2) were subconjunctivally delivered into the mouse eyes after injection of NV inducing agent. The pictures were taken 4 days after treatment. Panel e. presents the results of treatment with combined siRNA duplexes. Clearly, the LacZ-siRNA is an ideal control and has no effect on the neovascularization. All other treated eyes have very minimum NV and the treatment with the combined siRNA duplexes has the best result.

The same group of siRNA duplexes were also delivered by a systemic route with a targeted system called TargeTran. Figure 4 shows the systemic delivery of siRNA to inhibit NV in mouse eyes with TargeTran-siRNA. Complexes, (two for



each gene: mVEGF, mVEGFR1 and mVEGFR2) were IV administered for treatment of NV in mouse eyes. The pictures were taken 4 days after treatment. Panel e. presents results of treatment with combined siRNA duplexes. The siRNA-mediated inhibition of ocular neovascularization occurred almost exactly to that from local delivery treatment. The combined siRNA group provided the best result.

Quantitative results of changes with the angiogenesis area on each infected eye treated by different siRNA molecules, (targeting either single gene or multiple genes), have clearly demonstrated stronger inhibition of angiogenesis from the combined siRNA group. See Figure5, which shows a quantitative analysis of siRNA-mediated inhibition of NV TargeTranä- siRNA complexes (two for each gene: mVEGF,



mVEGFR1 and mVEGFR2) were IV administered for treatment of NV in mouse eyes. The pictures were taken 7 days after treatment. Panel e. shows result from treating with combined siRNA duplexes.

It is of course to be understood that the invention is not limited to the details of the embodiments which are described by way of example only.

All publications, patents and patent applications cited herein specifically are incorporated by reference in their entireties. The attached appendix specifically is incorporated as part of the present specification.

We claim:

1. A composition of two or more siRNA duplexes , wherein each duplex targets a different gene or gene product. and wherein the composition inhibits a disease process caused by abnormal over expression of at least one of the targeted gene or gene product by formation of a siRNA duplex.
2. The composition of claim 1, comprising at least three siRNA duplexes.
3. The composition of claim 1, comprising at least three gene sequences including three open reading frames and three mRNAs.
4. A method for ameliorating a disease caused at least in part by over expression of one or more disease genes as described in claim 3, comprising providing a composition of two or more siRNA duplexes, wherein each duplex targets a different gene or gene product. and at least one of the targeted gene or genes is a disease gene.
5. A composition as described in claim 1, in the form of a solution, particles, a mixture on a patch, or a powder in different textures.
6. The said combination can be used as therapeutic agent for treatment of various diseases by effective inhibition of over expression disease causing genes.
7. A composition as described in claim 1, in a form that can be administrated through various delivery routes including local injection, inhalation, topical cream, dermal patch, systemic delivery by IV, IP and IM.
8. A composition as described in claim 1, comprising an siRNA oligo cocktail (siRNA-OC).
9. siRNA-OC can be applied at the same time through the same route.
10. A composition as described in any of claims 1-9 for treating SARS coronavirus infection, comprising siRNA-OC that comprises one or more siRNA target sequences corresponding to: Spike protein, 21553-21573, aagctcctaattacactcaac; Nsp-9, 13530-13550, aaggatgaggaaggcaattta; nsp-10, 17544-17564, aaggataagtcagctcaatgc; nsp-13, 20843-20863, aactggcacactacttgtcga.
11. A composition as described in any of claims 1-9 for treating ocular neovascularization, comprising one or more siRNA duplexes: selected from the group consisting of mVEGFAa, AAGCCGTCCTGTGTGCCGCTG; mVEGFAb, AACGATGAAGCCCTGGAGTGC; mVEGFR1a, AAGTTAAAAGTGCCTGAACTG; mVEGFR1b,

AAGCAGGCCAGACTCTCTTTC; mVEGFR2a,
AAGCTCAGCACACAGAAAGAC; mVEGFR2b,
AATGCGGCGGTGGTGACAGTA.

12. The siRNA-OC can be applied with other drug modalities for treatment of diseases.
13. The siRNA-OC is particular useful for treatment of cancer, autoimmune and inflammatory diseases, and other diseases caused by abnormal over expression of multiple genes.
14. The combination of siRNA duplexes can be made with different chemistries with different backbones.

Application Data Sheet

Application Information

Application number::	Unassigned
Filing Date::	February 5, 2004
Application Type::	Utility
Subject Matter::	
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R?::	No
Number of CD disks::	
Number of copies of CDs::	
Sequence submission?::	No
Computer Readable Form (CRF)?::	No
Number of copies of CRF::	
Title::	siRNA Oligo Cocktail for Treatment of Cancer, Infectious and Inflammatory Diseases
Attorney Docket Number::	38147-0045
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	0
Small Entity?::	Yes
Latin name::	
Variety denomination name::	
Petition included?::	
Petition Type::	
Licensed US Govt. Agency::	
Contractor Grant Numbers::	
Secrecy Order in Parent Appl.?::	No

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